

## **REMARKS**

Claims 1-3, 6-10, 18, 24-26, 30-34, 44, and 46 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants thank the Examiner for renumbering added claims 47-53 to comply with 37 C.F.R. § 1.126. Applicants acknowledge that these claims are now numbered 58-64.

### **The Pun Declaration**

The Examiner argues that the declaration filed May 2, 2002, cannot be considered “because the date information is missing.” This position is, however, contrary to established U.S.P.T.O. procedure. The Examiner’s attention is drawn to MPEP 715.07, which discusses in detail the requirements of a declaration sufficient to swear behind a reference. In particular, that section states: “If the dates of the exhibits have been removed or blocked off, the matter of dates can be taken care of in the body of the oath or declaration. ... [I]f the applicant or patent owner does not desire to disclose his or her actual dates, he or she may merely allege that the acts referred to occurred prior to a specific date.” The Examiner has admitted that “the declaration asserts that the report, and in particular the date of the report (blacked out in submitted copy), supports the conclusion that the invention was taking place prior to the filing date of the first Kosak application (April 29, 1998).” Accordingly, Applicants submit that the declaration meets the requirements set forth in MPEP 715.07, and that the declaration must be considered as evidence of prior conception.

### **Informalities**

Claims 6, 24, and 30 have been amended as suggested by the Examiner. Certain claims dependent on claim 25 have also been amended for consistent use of the term “cyclodextrin monomer”. Reconsideration and withdrawal of this objection are respectfully requested.

The Claims Comply with 35 U.S.C. § 112

Claims 1-3, 6-10, 18, 24-25, 30-34, 44, 46, and 58-64 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner appears to be asserting that because purification details are not disclosed in exquisite detail, the written description is deemed to be incomplete. However, what is required by the most recent version of the *Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement*, which appeared in the Federal Register in January 2001, Vol. 66, No. 4, pp. 1104-1111, is only:

“sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., **or** by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus....”  
(emphasis added)

While the Examiner appears to be requiring physical and/or chemical properties, these are obviously not required by the Guidelines – the relevant structures have been disclosed, not to mention actual reduction to practice of several species within the claimed genus. Moreover, the purification of the subject polymers was well within the purview of a skilled artisan at the time the application was filed, and could be performed using routine technology like GPC as disclosed in the application without undue experimentation.

Accordingly, Applicants submit that the Examiner’s rejection is unfounded, both because the alleged grounds bear no relation to the written description requirement and because any failure to disclose purification details is nothing more than the omission of routine details that would be clear to a skilled artisan undertaking the purification process. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-2, 7-10, 18, 24-26, 31-34, 44, 46, and 58-64 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

In analyzing the Wands factors, the Examiner admits that the state of the art was well known, that the level of ordinary skill in the art was high, and that the level of predictability was also high. The Examiner conclusorily states that the breadth of the terms used in the claims is “clearly excessive,” and alleges that “the complete absence of other analytical data” and the lack of “complete description of the isolation procedures” “render the ordinary practitioner clueless” despite admitting that the experiments involved utilize “specific and well known in the art bifunctional reagents.” As argued above, purification of the subject polymers is a matter of routine experimentation and therefore does not detract from enablement. Any perceived lack of analytical data could easily be remedied by one of skill in the art performing the requisite analyses using routine techniques.

Equally importantly, none of these allegations detracts from the ability of one of skill in the art to make and use the subject polymers. As the Examiner admits, a wide variety of well known bifunctional reagents can be used to prepare the subject polymers. Similarly, in the admittedly “well known” state of the prior art, the preparation of bifunctional cyclodextrins that could be reacted with such bifunctional reagents to generate subject polymers had also been explored. The Examiner has failed to articulate a factual basis for the allegations raised in the Office Action that would negate the apparent ease with which one of skill in the art could prepare a wide range of polymers within the scope of the pending claims.

Indeed, Applicants have made of record a declaration under 37 C.F.R. §1.132 from Ron Breslow, indicating as his expert opinion that the present specification fully enabled one of skill in the art to vary the comonomer widely without resorting to undue experimentation in making or testing the resulting cyclodextrin copolymers.

As the Examiner had originally allowed very similar claims, the Examiner must have once agreed that the claimed subject matter was enabled. No evidence has been made of record that could justify the recent reversal of his position, or to rebut the evidence provided by Applicants in the Declaration of Ron Breslow. Accordingly, Applicants submit that the present rejection represents the very sort of arbitrary and capricious behavior chastised by the Federal Circuit in *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of Applicants' arguments of record, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 9, 10, and 31 are rejected under 35 U.S.C. § 112, second paragraph, because the phrase "whereby said ligand allows the therapeutic agent to target or bind to a cell" allegedly lacks proper antecedent basis in claim 1. Applicants have amended these claims to provide proper antecedent basis for all terms used. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-2, 7-10, 18, 24-27, 31-34, 44, and 46-53 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection.

Applicants respectfully direct the Examiner's attention to MPEP 2173.02: "Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made." As noted by MPEP 2173.02, "[t]he essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of particularity."

Applicants submit that the terms objected to by the Examiner are well understood in the art, and their scope can readily be ascertained by one of skill in the art based on the general teachings in the art and the context in which they are used in the specification. Breadth does not equate with indefiniteness, MPEP 2173.04, and it appears that the Examiner's objection stems from an unfounded desire to confine Applicants' invention more narrowly than is required by law.

As to claim 58, the Examiner suggests that the phrase "cyclodextrin derivative modified to bear one reactive site at each of exactly two positions" suggests a violation of valence rules. It is not clear how the Examiner has interpreted this phrase to give rise to this supposed violation, but when viewed in light of the specification, Applicants submit that this phrase plainly refers to a cyclodextrin derivative that has two functional groups reactive under polymerization conditions. Claims must be given their broadest reasonable interpretation. MPEP 2111. It appears the Examiner has, by his own acknowledgement, selected an illogical, and therefore unreasonable, interpretation, while shunning the readily apparent reasonable interpretation. Applicants may adopt a suggestion of the Examiner to rephrase claim 58 in a way that would allay his concerns, but as the Office Action does not clearly state the problem with this claim or how it might be corrected, Applicants maintain that the claim is clear and definite as written.

The Office Action suggests that functional language will not be tolerated in the claims. Applicants direct the Examiner's attention to MPEP 2173.01, which states that "Applicants may use functional language... or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. ... [A] claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought." Applicants submit that the pending claims define the subject matter in a way that would be clear to one of skill in the art.

For the reasons presented above, Applicants submit that the claims fully comply with 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

The Claims Comply with 35 U.S.C. § 102

Claims 1-3, 7, 59-60, and 62-64 are rejected under 35 U.S.C. §102(b) as being anticipated by Aldrich Catalog, 1994-1995. Applicants respectfully traverse this rejection.

The reference discloses a cyclodextrin/epichlorohydrin copolymer. This is similar to the polymer taught by Kosak, as discussed in greater detail below. Alone, this reference does not teach how to make or use the polymer being sold. However, Applicants acknowledge that such polymers had previously been disclosed in other publications, such as those by Pathi provided in Exhibit A.

As one of ordinary skill in the art would recognize, cyclodextrin molecules have multiple free hydroxyls that are capable of reacting with epichlorohydrin. Each epichlorohydrin has two reactive sites that can react with cyclodextrin molecules. As a result, reacting cyclodextrin molecules with epichlorohydrin results in a complex polymer network, because multiple epichlorohydrin molecules can react with each cyclodextrin molecule to create a polymer with multiple branching points. Although the modified cyclodextrin units taught in the present application facilitate the formation of linear polymers by permitting reaction at only two positions on each cyclodextrin unit, there is no way to exert this kind of control when unmodified cyclodextrin is used in the polymerization reaction.

The Aldrich Catalog neither teaches nor suggests a linear polymer, and does not enable the formation of linear polymer chains. Any linear polymers that might serendipitously have been present would have existed only as trace impurities and would not have been amenable to isolation even if they could have been detected.

Even if linear polymers were present in the composition offered by Aldrich as impurities, that fact would be insufficient to anticipate the presently claimed invention. The Supreme Court held, in *Tilghman v. Proctor*, 102 U.S. 707, 711, (1881) that “If the [claimed invention] were accidentally and unwittingly produced, whilst the operators were in pursuit of other and different results, without exciting attention and without its

even being known what was done or how it had been done, it would be absurd to say that this was an anticipation of Tilghman's discovery." Similarly, *International Nickel Co. v. Ford Motor Co.*, 166 F.Supp. 551, 560-61, (S.D.N.Y. 1958) held that "[w]here the allegedly anticipating product was produced merely by chance and never recognized or appreciated, one who later discovers and recognizes the product may patent it." The present situation falls squarely within this analysis. If indeed any linear cyclodextrin polymers were present in the Aldrich composition, they were created solely by chance, rather than by design. The catalog shows absolutely no recognition or appreciation of any linear polymers that may have been present. Accordingly, to hold the present claims anticipated by the Aldrich Catalog flies in the face of established Supreme Court precedent.

Particularly appropriate to the present situation, *Pfizer, Inc. v. International Rectifier Corp.*, 545 F. Supp. 486, 508, 207 USPQ 397 (C.D. Calif. 1980), *aff'd*, 635 F.2d 357, 217 USPQ 39 (9<sup>th</sup> Cir. 1982), *cert. denied*, 459 U.S. 1172 (1983) stands for the proposition that "it has never been the law that unrecognized or unappreciated coproduction of a small amount of a compound without a suggestion of that fact being shown in the prior art can be held as anticipating that compound." See also *In re Coordinated Pretrial Proceedings in Antibiotic Actions*, 498 F. Supp. 28, 35 (E.D. Pa. 1980). Thus, it is insufficient as a matter of law for the Examiner to assert that the present claims are anticipated because of some remote possibility – rather like monkeys typing Shakespeare – that a linear polymer might have been present as an impurity in the Aldrich composition.

For the reasons set forth above, Applicants submit that the present claims are novel over the art of record. Reconsideration and withdrawal of this rejection are respectfully requested.

The Claims Comply with 35 U.S.C. § 103(a)

Claims 1-3, 7-10, 18, 24-27, 31-32, 44, and 46 are rejected under 35 U.S.C. §102(e) or alternatively under 35 U.S.C. § 103(a) as being anticipated by Kosak '736.

Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The record so far contains arguments sufficient to nullify this rejection on several grounds that have either not been addressed by the Examiner or have been dismissed for reasons that go against established precedent and policy as set forth in case law and the MPEP. For convenience, these arguments are summarized here.

As already made of record, the disclosure of Kosak '736 is available as prior art only as of its filing date, December 30, 1998 – after the filing date of the parent to the present application, which fully supports the subject matter now being claimed. Accordingly, Kosak is potential prior art under 35 U.S.C. § 102(e) against the present application only to the extent of the disclosure of its parent application, U.S. Patent Application No. 09/067,921, filed April 29, 1998. Applicants provided the Examiner with a second copy of this application at the interview on January 31, 2003.

Again, Applicants point out that, as corroborated by the Breslow Declaration, the procedure set forth in the Kosak priority document would produce linear cyclodextrins only as a minor, unrecognized impurity, if at all. As described above with respect to the Aldrich Catalog, such teachings are insufficient as a matter of law to anticipate the presently claimed subject matter.

It is not clear of what relevance the definition of “leaving group” is to this issue, but Applicants respectfully submit that while leaving groups can be negatively charged or even neutral, one of skill in the art would not refer to a positively charged particle like a proton as a leaving group. Clarification is respectfully requested.

As a second ground for obviating the present rejection, Applicants again request further consideration of the declaration under 37 C.F.R. 1.131 filed May 2, 2002. The Examiner previously dismissed this declaration and accompanying Hwang report, as the Examiner has styled it, as not “extend[ing] to the subject matter of the Kosak et al. '736 reference.” In light of comments made by the Examiner in the subsequent Office Action, Applicants respectfully remind the Examiner that it is not necessary that the evidence



provided with such a declaration extend to the whole of the subject matter claimed. Such a declaration “must establish possession of either the whole invention claimed or something falling within the claim (such as a species of a claimed genus), in the sense that the claim as a whole reads on it. *In re Tanczyn*, 347 F.2d 830, 146 USPQ 298 (CCPA 1965) ... If the affidavit contains facts showing a completion of the invention commensurate with the extent of the invention as claimed is shown in the reference or activity, the affidavit or declaration is sufficient, whether or not it is a showing of the identical disclosure of the reference.... See *In re Wakefield*, 422, F.2d 987, 164 USPQ 636 (CCPA 1970). ... [A]pplicant’s possession of what is shown carries with it possession of variations and adaptations which would have been obvious, at the time, to one of ordinary skill in the art.” MPEP 715.02, emphasis added. Applicants submit that the Hwang report satisfies this standard, as discussed in greater detail below.

As previously argued, Applicants have identified only five pages of this priority document that discuss cyclodextrin polymers. Pages 12, 77, 88, and 102 refer only to cyclodextrin polymers generally, and neither teach nor suggest linear cyclodextrin copolymers having the structural and functional features recited in the present claims. Page 31 provides a synthesis protocol for a cyclodextrin polymer. At the interview on January 31, 2003, the Examiner expressed concern that some amount of linear cyclodextrin copolymer might be formed in this reaction. Applicants first direct the Examiner’s attention to the stoichiometry of this reaction – a five-fold excess of BDE to cyclodextrin is used. Thus, as corroborated by the previously submitted Declaration of Ron Breslow, the likelihood that a substantial number of cyclodextrins will be difunctionalized and capable of forming linear polymers is remote at best. Then, the BDE-modified cyclodextrins are treated with lysine to induce polymerization. Under these uncontrolled conditions, branched polymers will be formed instead of the linear cyclodextrin copolymers presently claimed. Any linear polymers that may form will be present only as trace impurities and will not be amenable to isolation even if they could be detected, as discussed above in relation to the similar polymer mentioned in the Aldrich Catalog.

Even if, contrary to the binding precedent of the judicial opinions cited again above, such disclosure were sufficient to render the present application anticipated or obvious if present in the prior art, Applicants submit that Kosak is not prior art against the present application in light of the declaration under 37 C.F.R. 1.131. The Hwang report included with the declaration teaches, at the very least, embodiments of the present invention that equal and far surpass any unwitting and accidental result that may be associated with the teachings of Kosak. See, for example, pages 22, 24, 28-30, and 33-34. Indeed, the Hwang report teaches the basic inventive concept – linear polymers of cyclodextrin – as Kosak does not. See *In re Spiller*, 500 F.2d 1170, 182 USPQ 614 (CCPA 1974). Accordingly, Kosak is simply not available as prior art against the present application.

Turning to the issue of obviousness, assuming Kosak were available as prior art against the present application, since Kosak neither teaches nor suggests the preparation of linear polymers, it cannot render the present claims obvious, either. No additional art has been cited that would overcome this deficiency.

For all the reasons presented above and already made of record, Applicants submit that the present claims are novel and non-obvious over Kosak. Reconsideration and withdrawal of this rejection are respectfully requested.

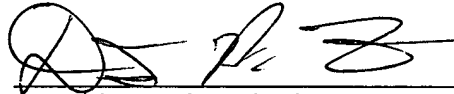
### CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. As suggested by Examiner Wilson in a telephonic interview, **Applicants respectfully request that all future communications from the Office in this case be reviewed by a supervisor prior to being mailed.** The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

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Respectfully Submitted,



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